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Short-term and long-term incidence of stroke in Takotsubo syndrome

The prognosis for patients diagnosed with Takotsubo syndrome (TTS) has generally been considered to be favourable. Nevertheless, recently published data indicate that TTS is associated with ventricular fibrillation, cardiogenic shock, right ventricular involvement, and thrombo-embolic events.[1]

Stroke is a similarly debilitating complication, which has been recognized to be increasingly relevant in acute coronary syndrome (ACS) patients,[2] thus prompting us to explore and compare the relationship of stroke in TTS patients too.

In our present analysis, we compared data from 138 consecutive TTS patients included from 2003 to 2017 and 532 consecutive ACS patients included from 2007 to 2008 and followed for 1448 ± 1255 days vs. 1373 ± 1294 days; $P = 0.54$. TTS patients were diagnosed according to the revised Mayo Clinic criteria.[3] Our study was conducted in accordance with the Declaration of Helsinki concerning investigations in human subjects, and the study protocol was approved by the Ethics Committee of the Medical Faculty of Mannheim, University of Heidelberg. The medical records of all patients were screened, and the follow-up was assessed by chart review and/or telephone review. The data are presented as means ± standard deviation for continuous variables with a normal distribution, as median (interquartile range) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. The Kolmogorov–Smirnov test was used to assess normal distribution. Student's *t*-test and the Mann–Whitney *U*-test were used to compare continuous variables with normal and non-normal distributions, respectively. The χ^2 test or Fisher's exact test was used to compare categorical variables. The log-rank test was used to compare the prevalence curves of stroke between the TTS group and the ACS group.

The baseline data as well as in-hospital events are outlined in *Table 1*. TTS patients showed a significantly lower ejection fraction at admission as compared with ACS patients (38 ± 8% vs. 51 ± 13%, $P = 0.01$). After 6 months, ejection fraction improved considerably in TTS patients (49 ± 12%). The TTS group consisted of 84.8% women. The medical history revealed no significant differences, except for the use of aspirin, which was significantly greater among ACS patients, and the use of angiotensin-converting enzyme inhibitors, which were more often prescribed in TTS patients.

Our data suggested that the relationship between TTS patients suffering from stroke and requiring respiratory support was statistically significant. Interestingly, although the rates of resuscitation, life-threatening arrhythmias, and use of inotropic agents as well as the duration of intensive care was higher in TTS patients as compared with ACS patients, this difference was not statistically significant.

Our current study revealed that the incidence of stroke was high among TTS patients as compared with ACS patients over a mean follow-up period of 5 years (*Figure 1*). The 30-day stroke rate in TTS was 2.9% as compared with 0.9% in ACS, $P = 0.07$, which increased to 6.5% vs. 3.2%, $P = 0.05$ over time. Interestingly, fewer TTS patients were treated with antiplatelet therapy at discharge (66.7% vs. 94.1%; $P = 0.07$), and the incidence of cancer in these patients was around 33.3% as compared with 5.9% in ACS patients with stroke ($P = 0.06$).

This study is the largest single-centre study comparing the incidence of stroke in TTS to ACS over a period of 5 years. Recent literature has suggested a higher incidence of acute stroke among TTS patients as compared with ACS patients.[1] Templin *et al*. reported about 2.4% acute stroke events. Although the underlying mechanism and pathophysiology contributing to this scenario is highly debatable, hypotheses have suggested association between stroke and acute thrombus formation in TTS patients.[4] Because several endothelial damage markers are increased in TTS patients, the role of endothelial dysfunction causing hyperviscosity and triggering thrombus formation has been discussed.[5]

An interesting aspect to be considered is the prevalence of malignancy in TTS patients and the increased incidence of stroke. As the stroke event could potentially occur anytime during the course of disease, the underlying pathophysiological mechanisms contributing to such a scenario are open to debate.

Recently published data have shown that CHA_2DS_2-VASc score might be a useful predictor of adverse events in TTS, including stroke. Patients were classified according to their CHA_2DS_2-VASc score into three groups: Groups A (≤ 1), B,[2,3] and C (≥ 4). A composite of death, myocardial infarction,

Table 1 Baseline characteristics of 9 patients with TTS and 17 patients with MI with stroke

Variables	Overall TTS (n = 138)	Overall MI (n = 532)	TTS with stroke (n = 9)	MI with stroke (n = 17)	P value*
Demographics					
Age, mean ± SD	67 ± 11	68 ± 13	73 ± 9	75 ± 9	0.94
Female (%)	117 (84.8)	190 (35.7)	5 (55.6)	12 (70.6)	0.44
Symptoms, n (%)					
Dyspnoe	54 (39.1)	139 (26.1)	2 (22.2)	3 (17.6)	0.78
Chest pain	69 (50.4)	403 (75.8)	4 (44.4)	13 (76.5)	0.10
Clinic parameter					
Systolic BP, mmHg median (IQR)	141 (62–240)	139 (0–280)	151 (118–220)	162 (110–240)	0.47
Diastolic BP, mmHg median (IQR)	79 (40–151)	78 (0–400)	88 (60–100)	88 (65–150)	0.92
Heart rate, b.p.m. mean ± SD	99 ± 26	91 ± 23	93 ± 21	77 ± 20	0.26
ECG data, n (%)					
ST-segment elevation	41 (29.9)	222 (41.9)	3 (33.3)	7 (41.2)	0.70
Inversed T-waves	123 (93.2)	245 (46.3)	9 (100.0)	7 (41.2)	**<0.01**
PQ interval	159 ± 28	168 ± 36	164 ± 23	172 ± 28	0.62
QTc (ms)	475 (62)	446 (358–614)	471 (258–598)	460 (410–569)	0.30
Laboratory values, median (IQR)					
Troponin I (U/L) (IQR)	63.15 (0.01–2738.00)	22.45 (0.02–1704.00)	2.86 (0.17–7.53)	19.14 (0.44–156.42)	0.15
Creatine phosphatkinase (U/L) (IQR)	587 (39–26600)	1166 (23–20149)	665 (43–4478)	1323 (110–13925)	0.33
CKMB (U/L) (IQR) (Creatine kinase-myocardial-type)	35 (1–415)	80 (0–970)	35 (1–415)	62 (5–868)	0.48
C-reactive protein (mg/L) (IQR)	48.2 (0.4–467.1)	40.7 (0.0–594.0)	33.5 (2.7–90.7)	40.7 (1.6–147.9)	0.51
Haemoglobin (g/dL) mean ± SD	12.2 ± 2.0	12.1 ± 2.3	13.1 ± 2.4	13.3 ± 1.6	0.70
Creatinine (mg/dL) (IQR)	1.12 (0.40–5.56)	1.26 (0.22–12.16)	1.59 (0.70–5.12)	1.05 (0.60–1.54)	0.11
Echocardiography data, n (%)					
LVEF %, mean ± SD	39 ± 10	49 ± 14	38 ± 8	51 ± 13	**0.01**
LVEF% follow-up, mean ± SD	52 ± 11	49 ± 14	49 ± 12	51 ± 13	0.75
Mitral regurgitation	66 (47.8)	152 (28.6)	7 (77.8)	5 (29.4)	**0.02**
Moderate	56 (40.6)	118 (22.2)	5 (55.6)	5 (29.4)	
Severe	10 (7.2)	34 (6.4)	2 (22.2)	0 (0.0)	
Tricuspid regurgitation	54 (39.1)	69 (13.0)	4 (44.4)	2 (11.8)	0.06
Moderate	48 (34.8)	57 (10.7)	4 (44.4)	2 (11.8)	
Severe	6 (4.3)	12 (2.3)	0 (0.0)	0 (0.0)	
Medical history, n (%)					
Smoking	41 (29.7)	198 (37.2)	3 (33.3)	7 (41.2)	0.70
Diabetes mellitus	31 (22.5)	170 (32.0)	3 (33.3)	8 (47.1)	0.50
BMI > 25 kg/m^2	36 (31.3)	271 (50.9)	2 (22.2)	7 (41.2)	0.96
Hypertension	82 (59.4)	361 (67.9)	9 (100.0)	15 (88.2)	0.28
COPD	28 (20.3)	38 (7.1)	1 (11.1)	1 (5.9)	0.63
Atrial fibrillation	26 (18.8)	76 (14.3)	2 (22.2)	4 (23.5)	0.94
Paroxysmal	17 (12.3)	43 (8.1)	0 (0.0)	2 (11.8)	
Persistent	6 (4.3)	17 (3.2)	1 (11.1)	1 (5.9)	
Permanent	4 (2.9)	16 (3.0)	1 (11.1)	1 (5.9)	
History of malignancy	28 (20.3)	32 (6.0)	3 (33.3)	1 (5.9)	0.06
Drugs on admission, n (%)					
Beta-blocker	46 (35.4)	173 (32.8)	2 (22.2)	6 (35.3)	0.61
ACE inhibitor	51 (39.2)	146 (27.5)	6 (66.7)	4 (23.5)	**0.01**
Aldosterone inhibitor	1 (0.8)	4 (0.8)	0 (0.0)	0 (0.0)	1.00
Aspirin	36 (27.7)	154 (29.1)	5 (55.6)	7 (41.2)	0.32
Anticoagulation	12 (9.3)	36 (6.8)	1 (11.1)	1 (5.9)	0.57
Drugs on discharge, n (%)					
Beta-blocker	103 (74.6)	422 (79.3)	6 (66.7)	15 (88.2)	0.18
ACE inhibitor	82 (59.4)	349 (65.6)	9 (100.0)	11 (64.7)	**0.04**
Aldosterone inhibitor	2 (1.4)	7 (1.3)	0 (0.0)	0 (0.0)	1.00
Aspirin	53 (38.4)	458 (86.1)	6 (66.7)	16 (94.1)	0.07
Anticoagulation	33 (23.9)	77 (14.5)	2 (22.2)	3 (17.6)	0.78

ACE, angiotensin-converting enzyme; BMI, body mass index, disease; BP, blood pressure; COPD, chronic obstructive pulmonary; ECG, electrocardiogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SD, standard deviation; TTS, Takotsubo syndrome.
*P values for the comparison between TTS with stroke and MI with stroke; only comparing patients with stroke.

and stroke rate in the three groups was shown to be 6%, 9%, and 17% in Groups A, B, and C, respectively (P = 0.033).[6]

Although current knowledge explaining the underlying pathophysiology of TTS and its association with stroke still leaves room for further interpretation and speculation, data about treatment strategy are still lacking. The overall incidence of stroke in TTS patients as compared with ACS patients is significantly increased in the acute situation as well as years after the primary TTS event. Additionally, in concordance with previous data, TTS patients suffering from cancer

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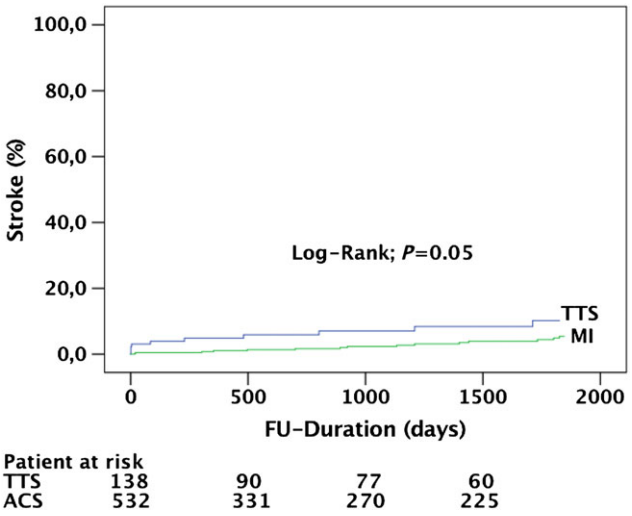
Figure 1 Kaplan–Meier analysis of Takotsubo syndrome (TTS) vs. consecutive myocardial infarction (MI) patients. FU, follow-up.



had impaired outcomes and more cardiovascular events, including stroke, as compared with TTS patients without cancer.[7,8] This and the fact that stroke incidence is higher in TTS as compared with ACS patients (where incidence of cancer was lower) could help confirm the hypothesis that stroke is essentially triggered by the cancer and that TTS is just an 'innocent bystander'. In this regard, recently published data suggest that antiplatelet therapy reduces major adverse cardiovascular events in TTS patients.[9]

Thus, TTS patients suffering from cancer might be considered as a high-risk subgroup because of the increased incidence of stroke at long-term follow-up. The limitation of this single-centre study and its low number of events might prompt investigation of the incidence of thrombo-embolic events in TTS in acute situations as well as in the long term.

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